# Comparison between Medical Management, Enhanced External Counterpulsation (EECP) and Cardiac Resynchronization Therapy (CRT) in Heart Failure

Majid Maleki[1] MD, Sepideh Pezeshki[2] MD, Seyyed Mohammad Fereshtehnejad MD

## Abstract

***Introduction***- The clinical syndrome of heart failure (HF) remains a leading cause of cardiac morbidity and mortality. The coming years will see a continuous growth in the epidemic of HF and increasingly complex pharmacological, interventional, and device-based therapies, effective in reducing HF morbidity and mortality. Highly trained clinician-specialists are needed to assist in optimally evaluating and managing patients with HF.

***Objective***- The aim of the present study was to determine the best management protocol for HF by surveying different therapeutic protocols (medical, cardiac resynchronization therapy [CRT] program, and enhanced external counterpulsation [EECP]).

***Methods***- Initial assessment was performed for a total of 280 HF patients evaluated in the Heart Failure Clinic. Eighty patients were included in the study; the selection being done in accordance with the inclusion criteria of ejection fraction (EF) ≤35%. By surveying different therapeutic protocols, disease management programs (DPMs), namely medical, CRT, and EECP, were performed in three study groups: group A; medical therapy (n=37), group B; EECP (n=16), and group C; CRT (n=27). Changes in New York Heart Association (NYHA) functional class and echocardiographic indexes were evaluated in the three groups.

***Results***- There was no significant change in EF, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and E/E' ratio after medical therapy. There was, however, a significant improvement in NYHA function class (P <0.001). EECP significantly improved EF (P<0.05) and E/E' ratio (P<0.001). There was also a significant reduction in LVESV (P<0.05) with improvement in NYHA functional class and rehospitalization (P<0.001). CRT significantly reduced LVESV, LVEDV (P<0.05), E/E' ratio (P<0.001), and EF (P<0.001).There was improvement in NYHA functional class and rehospitalization as well (P<0.001).

***Conclusion***- Our findings suggest that disease management programs or guideline-based treatments reduce first hospitalization and rehospitalization rates in patients with heart failure and improve NYHA functional class and the echocardiographic findings of LVESV, LVEDV, LVEF, and E/E' ratio. In the hope of improving HF outcomes, disease management programs (medical care, EFCP, CRT-D implantation, etc.) have been developed to standardize and optimize HF treatment, focusing on disease education for the patient and continuing support after hospital discharge ***(Iranian Heart Journal 2008; 9 (3):25 -36).***

**Key words:** heart failure (HF) ■ disease management programs ■ enhanced external counterpulsation ■ cardiac resynchronization therapy

Heart failure (HF) remains one of the most common, costly, disabling, and deadly medical conditions encountered by a wide range of physicians and surgeons in both primary and secondary care.

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1. Professor in Cardiology, and 2, Cardiologist, Shaheed Rajaie Cardiovascular Medical Center, Iran University of Medical Sciences and Health Services, Tehran, Iran

Corresponding author: M. Maleki, M.D., Dept. of Cardiology, Shaheed Rajaie Cardiovascular Medical Center, Iran University of Medical Sciences and Health Services, Tehran, Iran Tel: 02122055594

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Understanding of its epidemiology, pathophysiology, diagnosis, and, especially treatment has advanced greatly during the past 20 years and continues to develop rapidly.[1]

Between 1% and 2% of the adult population may develop HF, although it mainly affects elderly people: 6–10% of people over the age of 65 have this disorder.[2-11] The lifetime risk of developing HF is roughly one in five for a person aged 40 years.[12,13] The age-adjusted incidence of HF has remained stable over the past 20 years,[14,15] but prevalence is thought to be increasing.[16] Each year, about two individuals per thousand of the adult population are discharged from hospital with HF, which accounts for about 5% of all medical and geriatric admissions and is the single most common cause of such admissions in people aged over 65.[17-23]

Nowadays, HF is the reason for at least 20 percent of all hospital admissions among those older than 65.[24] An understanding of the pathophysiology and natural history of heart failure underpins the therapeutic approaches used to achieve the goals of treatment, which are to relieve symptoms, avoid hospital admission, and prolong life. On the basis of a large number of randomized controlled trials, drugs are the mainstay of treatment in all patients with heart failure and reduced left-ventricular systolic function. How care is organized and delivered can also influence outcome,[25] and there is some evidence that exercise is beneficial.[26-28] End points of large randomized trials now include the effect of intervention on the rate of hospital admissions. For example, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta blockers, spironolactone, biventricular pacing, coronary artery bypass surgery (CABG), and the use of multidisciplinary teams to treat HF have all shown to reduce the rate of hospitalization substantially and that of mortality improving functional status.[24] There has lately been intense interest in implantable devices and surgery for selected patients with this type of HF. The evidence base for treatments other than drugs, devices, and surgery is poor.

Cardiac resynchronization therapy (CRT) is a recently developed technique in which biventricular pacing is used to improve the ventricular function. Preliminary reports from two randomized trials indicate that combining cardiac resynchronization with defibrillator therapy may improve functional status and lower mortality.[29] CRT is established as adjunctive treatment for patients with systolic HF and ventricular dyssynchrony; the majority of recipients respond to CRT with improvements in quality of life, New York Heart Association (NYHA) functional class, 6-min walk test, and ventricular function.[30-32]

On the other hand, enhanced external counterpulsation (EECP) is a noninvasive, pneumatic technique that utilizes electrocardiogram-gated diastolic inflation of a series of lower-extremity cuffs to effectively increase diastolic and mean intracoronary pressures as well as coronary flow, while reducing systolic pressure in the central aorta and the coronary artery.[33] In addition, EECP improves diastolic filling, decreases left ventricular (LV) end-diastolic pressure, and improves LV peak filling rate, end-diastolic volume, and time-to-peak filling rate.[34] Although EECP is known to decrease symptoms in patients with angina, its role in the treatment of patients with HF has only recently been investigated. Recent studies suggest that EECP increases exercise capacity and improves functional status and quality of life in patients with HF. In light of these findings, FDA cleared EECP therapy for the treatment of HF in 2002.[35-39]

Despite using different options for HF management, the coming years will see continued growth in the epidemic of HF and increasingly complex pharmacological, interventional, and device-based therapies, effective in reducing HF morbidity and mortality. Therefore highly-trained specialists are needed to assist in optimally evaluating and managing patients with HF.[40]

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Consequently, the aim of this study was to determine the optimal care of patients with HF in accordance with disease management programs by surveying different therapeutic protocols, namely medical, CRT, and EECP.

## Methods

### Patients

In order to accurately assess disease management programs (DMPs) in HF, we evaluated all patients who had been referred to the Heart Failure Clinic of Shaheed Rajaie Hospital, Tehran, Iran (June 2004 to May 2007). We devised a treatment algorithm in order to assess and treat symptomatic HF and low left ventricular ejection fraction (LVEF) at the clinic. The following three components of a complete diagnosis were the best keys to the selection of patients: firstly, the etiology should be clearly established; secondly, the hemodynamic mechanism should be adequately investigated and understood; and thirdly, the degree of current limitations must be correctly staged (NYHA class).

From a total of 280 cases, 80 patients were included in the study. All the patients had EF≤35% and cardiomyopathy, and there was no history of renal failure, hepatic failure, and secondary HF (hyperthyroidism, anemia, etc.). The patients at this stage were divided into two groups: patients with angina and any evidence suggestive of coronary artery disease and patients with documented cardiomyopathy (ischemic, dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy). In patients with angina, after history taking and initial evaluation of rest ECG, myocardial perfusion imaging or stress echocardiography was requested. If there was viable tissue, selective coronary angiography was done. If the patient was suitable for revascularization, CABG was carried out; and if the patient was not suitable for CABG, EECP with optimal medical therapy was recommended. If the patient was not suitable for EECP or did not respond to it or refused it, tissue Doppler imaging echocardiography was requested. If the patient was suitable for CRT implantation, the procedure was performed; and if the patient was not suitable or refused, optimal medical therapy and follow-up was recommended. Finally, when the patient had refractory symptoms, heart transplantation was considered.

In the second group, after optimal medical management, if the patients continued to have refractory symptoms, tissue Doppler echocardiography was requested; and if the results were favorable, CRT implantation was done. The patients who had refractory symptoms became candidates for heart transplantation. Finally, the patients were divided into three groups:

group A: 37 patients who underwent medical therapy,

group B: 16 patients who underwent EECP, and

group C: 27 patients who underwent CRT.

### Assessment

Cardiovascular events such as cardiovascular surgery or percutaneous transluminal coronary angioplasty (PTCA), thrombolysis or primary angioplasty, risk profile, current therapy, response to previous therapy, other systemic disease, and comorbidities were all questioned. In physical examination, symptoms such as dyspnea, fatigue, angina, edema, and signs such as appearance, heart rate, blood pressure, jugular venous pressure, hepatic congestion, presence of S3 and/or S4, gallop rhythm, peripheral edema, pleural and/or pericardial effusion, ascites, weight, height, and body mass index (BMI) were all recorded.

At rest, electrocardiography was performed and variables like rate, rhythm, dysrhythmia, hypertrophy, ischemia changes, QRS duration, PR interval, and QT interval (if necessary) were determined. A chest X-ray was also used to evaluate heart size, pulmonary venous congestion, interstitial and alveolar edema, pneumonia, and pleural

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effusion. Additionally, laboratory tests of serum hemoglobin, hematocrit, blood count, renal function tests, blood sugar , lipid profile, liver function, and thyroid function tests (if necessary) were recorded.

**Echocardiography**

Standard echocardiography was carried out in accordance with the American Society of Echocardiography using a digital ultrasound machine (Vivid 3, Vivid 7) with the patient in the left lateral decubitus position. A variable frequency phased-array transducer (2.3-3.5-4.0 MHz) was used for two dimensional, M-mode, and Doppler imaging. All the measurements were analyzed using the average of 3 cardiac cycles. Two-dimensional (2D) measurements of LVEF were calculated using a modified Simpson's method. Pulsed Doppler assessment of LV inflow was performed in the apical 4-chamber view with the sample volume placed at the level of the valve tips. The following measurements of global diastolic function were determined: peak velocity of E and A waves and the E/A ratio deceleration time of the E wave (msec); and isovolumic relaxation time (msec), measured as the time interval occurring between the end of systolic output flow and transmitral E-wave onset by placing the pulsed Doppler sample volume between the outflow tract and the mitral valve. Finally, LVEF, MR, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and E/E' were evaluated. Echocardiography was performed at the beginning and at the end of our study.

**Pulsed Doppler myocardial imaging**

Pulsed Doppler myocardial imaging (DMI) was performed by spectral pulsed Doppler signal filter by adjusting the Nyquist limit within 25-20 cm/sec (close to myocardial velocities) and using minimal optimal gain. In the apical 4-chamber view, a 3.5-mm pulsed Doppler sample volume was placed on the basal septum of the LV at the level of the mitral annulus. Myocardial systolic wave (S) and early diastolic wave (Ea) were measured.

**Diastolic function grading**

Normal LV diastolic function was diagnosed if the peak early diastolic transmitral flow velocity [E/ peak late diastolic transmitral flow velocity (A)] ratio was between 0.75 and 1.5 and the E/Ea ratio was <8. Mild LV diastolic dysfunction was diagnosed if the E/A ratio was <0.75 regardless of the E/E' ratio. Moderate LV diastolic dysfunction was diagnosed if the E/A ratio was between 0.75 and 1.50 and the mitral E/peak early diastolic myocardial velocity (E') ratio was >8. Severe LV diastolic dysfunction was diagnosed if the E/A ratio was >1.5 and E/E' ratio was >10.

**Treatment**

To determine the therapy of choice in each patient, they were categorized in four stages. Control of risk factors in stage A (e.g. hypertension, CAD, and diabetes mellitus) has a favorable effect on the incidence of future cardiovascular events. Patients with stage A HF are at high risk for HF but do not have structural heart disease or symptoms of HF.[24] Patients with stage B HF have structural heart disease but have no symptoms of HF (e.g. left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction, or valvular heart disease). All of these patients are considered to have NYHA class I symptoms. Patients with stage C HF have known structural heart disease and current or previous symptoms of HF; their symptoms may be classified as NYHA class I, II, III, or IV. Patients with stage D HF have refractory symptoms of HF at rest despite maximal medical therapy, are hospitalized, and require specialized interventions.[24]

The goals of therapy for patients with HF and a low EF are to improve survival, slow the progression of disease, obviate symptoms, and minimize risk factors. Modification of life style can be helpful in controlling the symptoms of HF. For example, basic habits of moderate sodium restriction, weight

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monitoring, and adherence to medication schedules may aid in avoiding fluid retention or alerting the patient to its presence. Moderation of alcohol intake is advised, and avoidance of non-steroidal anti-inflammatory drugs is also important. For selected patients, a regularly scheduled exercise program may have beneficial effects on symptoms.[24] ACE inhibitors are recommended for many patients with stage A and all patients with stage B, stage C, or stage D. Beta blockers have long been used for the treatment of hypertension, angina, and arrhythmias as well as prophylaxis in patients who have had a myocardial infarction.[40] There is evidence to support the use of spironolactone and aldosterone antagonists in patients with advanced symptoms of HF, specifically, NYHA class III or IV symptoms. Since HF is a salt-avid syndrome resulting in intravascular volume overload, diuretics are the mainstay for controlling the symptoms of congestion. Thiazide or loop diuretics are often prescribed. No difference has been reported in mortality between patients receiving digoxin and patients receiving placebo; however, there are reports of a decrease in the rate of worsening HF and hospitalization.[39-42]
Additionally, vaccination against influenza and pneumococcal infection is recommended in vulnerable individuals, including HF patients in whom these infections can deteriorate their cardiac function leading to hospital admission.[41] Antiplatelet treatment is generally recommended in patients with ischemic cardiomyopathy.[41-43]

**Enhanced external counterpulsation (EECP)**

EECP is a noninvasive, pneumatic technique that utilizes electrocardiogram-gated diastolic inflation of a series of lower-extremity cuffs to effectively increase diastolic and mean intracoronary pressures as well as coronary flow, while reducing systolic pressure in the central aorta and the coronary artery.[38,45-47]
The patients assigned to EECP with NYHA functional class II-III symptoms secondary to ischemic cardiomyopathy and LVEF≤35% with optimal medical therapy received thirty-five 1-hr sessions over a period of 7 to 8 weeks. Three pneumatic cuffs were placed around the lower limbs and buttocks and were inflated sequentially upward at the onset of diastole, and released rapidly and simultaneously before the onset of systole. The protocol-specified applied pressure was 300mmHg and was reached within 5 minutes of the initiation of treatment. Pulse oximetry was monitored continuously during the treatment session, and the subjects' clinical status was re-evaluated if the oxygen saturation dropped by ≥4%.

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**Cardiac Resynchronization Therapy (CRT)**

Indications for CRT are based on the American College of Cardiology, American Heart Association, and Heart Rhythm Society guidelines, which recommend CRT for NYHA functional class III or IV HF refractory to pharmacological therapy and having QRS duration >130ms, EF ≤35% and LVED dimension >55mm.[48-52] Three transvenous pacing leads were inserted, one in the right atrium and another on the high interventricular septum or in the right ventricular outflow tract. In addition, a coronary sinus lead was positioned on the LV free wall through a coronary sinus tributary. The location of the LV-pacing lead was in the lateral vein in 70% and in the posterolateral vein in the remaining 30%. After implantation, the atrioventricular interval was optimized for maximal diastolic filling using Doppler echocardiography.

**Follow-up**

The follow-up of the patients was done in accordance with the step-by-step method as recommended by McMurray.[44]
Step 1: Consider in all patients with NYHA class II-IV, ACE inhibitors, beta blockers, angiotensin receptor blockers, implantable-cardioverter defibrillators, and amiodarone, digoxin, and warfarin if there is atrial

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fibrillation or history of arrhythmia and any evidence of a clot formation.

Step 2: If there are persisting signs and symptoms (NYHA class III-IV), consider aldactone, CRT, and digoxin.

Step 3: If there is intractable HF (NYHA II-IV), consider heart transplantation and ventricular assist device.

The patients in all the three treatment groups were seen during the follow-up at weeks 1 and 3 and month 6 after treatment. A second echocardiography was performed at the end of the follow-up period in all the patients.

### Statistical analysis

All the data are expressed as mean ±SD. The distribution of nominal variables was compared using the Chi-square test. In order to compare the mean values of the quantitative variables, the independent T-test and one-way ANOVA procedures or their non-parametric equivalents (Mann-Whitney U-test and Kruskal-Wallis) were performed. To evaluate the changes of echocardiographic indexes and NYHA class, before and after treatment, the paired T-test and sign T-test were performed in each group of study, respectively. To better assess the factors that may be related to the changes of main variables of the study, correlation was also used. In comparison between the groups, a post-hoc Tukey test was performed. Kaplan–Meier survival analysis was employed to calculate the mean survival time to encounter the need for transplantation among the patients.

In all the statistical procedures, a two-sided P-value<0.05 was considered statistically significant.

### Results

Eighty consecutive patients referred to the Heart Failure Clinic were evaluated according to our DPM algorithm and were divided into 3 main groups: group A, medical therapy (n=37); group B, EECP (n=16), and group C, CRT (n=27).

**Group A (medical therapy)**

This group of 37 patients comprised 9 (24.3%) females and 28 (72.7%) males with a mean age of 55.49 (SD 13.73) years, ranging from 17 to 83 years, and with a mean body mass index (BMI) of 25.28 (SD 3.88) $kg/m^2$, ranging from 19.4 to 37.6 $kg/m^2$. The demographic, clinical, and laboratory characteristics of the patients in group A are listed in Table I. The most common symptoms were easy fatigability (89.2%) and dyspnea (83.8%). The most frequent drugs used in group A were carvedilol (94.6%), ACE inhibitor (86.5%), and furosemide (81.1%).

The mean echocardiographic indices, before and after treatment are shown in Table II. The mean baseline EF and E/E' ratio were 22.03% (SD 8.33) and 14.89% (SD 5.09), respectively; they were changed to 22.4% (SD 8.8) and 14.5% (SD 5.0), respectively. Be that as it may, these changes were not statistically significant (P>0.05). Table II and Fig. 1 show that in addition to EF and E/E', the reductions in LVESV and LVEDV were not significant (P>0.05) either.

The most common types of diastolic dysfunction in the patients of group A were irreversible restrictive (54.1%), reversible restrictive (24.3%), and pseudonormalization (16.2%). The frequency of different NYHA functional class of HF before and after treatment is also depicted in Table II. At baseline, the frequency of class II was 35.1%; class III, 59.5%; and class IV, 5.4%, which changed to class II, 83.8%; class III, 13.5%; and class IV, 2.7%. This improvement was statistically significant (P<0.001). Further analysis showed a significant direct correlation between the change in E/E' after therapy and body weight ($P=0.03$, $r_{Spearman} = 0.384$).

Finally, at 28-month follow-up in this group, 20 (54.1%) patients were candidates for heart transplantation and 1 patient died. The

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survival graph of the patients who underwent only medical therapy (group A) to encounter need for transplantation is illustrated in Fig. 4. Mean survival time to encounter need for transplantation was estimated at 26.31(SD=1.39) months.

**Group B (EECP)**

This group of 16 patients was comprised of 4 (25%) females and 12 (75%) males with a mean age of 58.13(SD 11.68) years, ranging from 40 to 83 years, and with a mean BMI of 25.02 (SD 2.39) Kg/m,$^2$ ranging from 21.6 to 31.2 Kg/m$^2$. More demographic, clinical and laboratory characteristics of the patients in group B are listed in Table I. The most common symptoms were easy fatigability (93.8%) and dyspnea (93.8%).

The mean echocardiographic indices, before and after treatment, are shown in Table II.

Fig. 1 illustrates that the mean EF was significantly increased [from 26.03% (SD 7.63) to 28.41% (SD 7.69), P=0.008] and the mean of E/E' ratio was significantly decreased [from 15.46 (SD 7.18) to 13.76 (SD 5.67), P=0.001] after EECP. However, the changes in LVESV and LVEDV were not significant (P>0.05). The most common types of diastolic dysfunction in the patients of group B were pseudonormalization (43.8%), reversible restrictive (37.5%), and impaired relaxation (12.5%).

NYHA functional class was also significantly improved after EECP (P<0.001). Table II shows that at baseline, the frequency of class II was 12.5%; class III, 81.3%; and class IV, 6.3%, which changed to class II, 93.8%; and class IV, 6.2%.

Further analysis showed that there were significant correlations between the change in EF after EECP and Hb (P=0.046, $r_{Pearson}$ =0.584), BS (P=0.049, $r_{Pearson}$ =0.578), and blood Na concentration (P=0.031, $r_{Pearson}$ =0.622). The change in LVESV was correlated significantly with Hb (P=0.025, $r_{Pearson}$=0.639), BS (P=0.013, $r_{Pearson}$=0.692), BUN (P=0.005, $r_{Pearson}$=0.755), and blood Na concentration (P=0.028, $r_{Pearson}$=0.630). The change in LVEDV was also correlated with Hb (P=0.011, $r_{Pearson}$ =0.702), BS (P=0.001, $r_{Pearson}$ =0.809), blood Na (P=0.049, $r_{Pearson}$ =0.578), and K concentration (P=0.035, $r_{Pearson}$ =0.611).

Moreover, the decrease in the E/E' ratio was significantly higher in the patients with baseline E/E'≥14 [2.77 (SD 1.62) vs. 0.33 (SD 0.36), P=0.002].

**Group C (CRT)**

In the group managed with CRT, there were 27 patients, consisting of 21 (77.8%) males and 6 (22.2%) females. The mean age was 57.07 (SD 13.28) years, and the mean BMI was 25.95 (SD 4.49) Kg/m$^2$. The demographic, clinical, and laboratory characteristics of the patients in group C are listed in Table I. The most common symptoms were easy fatigability (92.6%) and dyspnea (77.8%).

The mean echocardiographic indices, before and after treatment, are shown in Table II. As Fig. 1 illustrates, all of the indices were significantly changed after CRT except LVEDV. The mean EF was significantly increased [from 17.87% (SD 5.87) to 21.28% (SD 6.28), P<0.001], the mean E/E' ratio was significantly decreased [from 20.31 (SD 7.40) to 15.68 (SD 5.26), P<0.001], and the mean LVESV was significantly decreased [from 174.63 (SD 79.94) to 157.44 (SD 67.38), P=0.016] after CRT implantation. The most common types of diastolic dysfunction in the patients of group C were reversible restrictive (51.9%), pseudonormalization (25.9%), and irreversible restrictive (18.5%).

NYHA functional class was also significantly improved after CRT (P<0.001). Table II demonstrates that at baseline, the frequency of class III was 92.6% and class IV was 7.4% (without class II), which changed to class II, 92.6%; class III, 3.7%; and class IV, 3.7% after CRT.

Further analysis showed that there were significant correlations between the change in EF after CRT and blood K concentration (P=0.016, $r_{Pearson}$=0.467). The change in

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LVESV was correlated significantly with Cr (P=0.006, $r_{Pearson}$= -0.523), LDL (P=0.043, $r_{Pearson}$= -0.400), and blood K concentration (P=0.018, $r_{Pearson}$= -0.459). The change in LVEDV was also correlated with Cr (P=0.004, $r_{Spearman}$ = -0.541).
Moreover, the decrease in the E/E' ratio was significantly higher in the patients with baseline E/E'≥14 [5.85 (SD 4.12) vs. 1.14 (SD 0.87), P<0.001] who underwent CRT implantation. At 6-month follow-up, one patient (3.7%) died in group C.

**Comparison between groups**

Although the patients' criteria were not similar between the different groups of the study, the results were compared. As Fig. 2 demonstrates, the mean changes and improvements in different echocardiographic indexes were significantly higher in group C (CRT). NYHA class was also significantly more improved in group C (CRT) in comparison with the other two groups of study (P<0.001, Fig. 3). In group C, 96.3% of the patients had improvements in their NYHA class; whereas this ratio was 87.5% and 48.6% in groups B and A, respectively.

## Discussion

This study is one of the first studies on DMPs (guideline-based treatment) conducted in our center in order to improve HF outcomes and standardize and optimize treatment. We sought to visit patients step-by-step according to an algorithm and show the efficiency of DMPs with NYHA functional class improvement, reduced rehospitalization, and echocardiographic parameters of EF, LVEDV, LVESV, and E/E'. Our findings demonstrated that DPMs significantly improved NYHA functional class and reduced rehospitalizations (P<0.001).
Our findings chime in with those of Gohler et al. in their systemic meta-analysis for rehospitalization, quality of life, and NYHA class. They showed that DMPs had the potential to reduce mortality and morbidity in HF patients.[40]
In group A (medical therapy), there were no significant changes in EF, LVESV, LVEDV, and E/E' after medical therapy (P>0.05). Nevertheless, a comparison between baseline and after treatment EF showed an increase in EF, which should not be ignored despite the fact that it was not statistically significant (P=0.07).
On the other hand, there was a significant relationship between body weight and decrease in E/E' in this group, which was compatible with textbooks,[53] stating that obesity may confer more favorable prognosis in patients with advanced HF.
In group B (EECP therapy), there was a significant improvement in LVEF and E/E' ratio (P<0.05), which was in line with a recent study in our center, demonstrating a significant change in LVEF, $EDV_1$, and ESV with P<0.05 in ischemic cardiomyopathy, especially in patients with higher E/E'≥14. This is compatible with all other previous studies such as PEECH (prospective evaluation in ischemic and non-ischemic cardiomyopathy) study, too.[38] In addition, there was a significant relationship between BS, BUN, and Hb levels and the patients' response to EECP (P<0.05). This is also concordant with previous findings indicating that chronic anemia is associated with a reduction in systemic vascular resistance and a decrease in arteriolar tone and blood viscosity, thus playing an important role in the pathophysiology of HF.[53] Moreover, there is a relationship between a variety of biochemical measurements and clinical outcomes.[53]
The PEECH study assessed the benefits of EECP in the treatment of patients with mild to moderate HF. In this randomized, single-blinded study, EECP improved exercise tolerance, quality of life, and NYHA functional classification without an accompanying increase in peak $VO_2$.[38] Furthermore, EECP improved exercise capacity and quality of life without adverse

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consequences in a small group of patients with stable HF who underwent 35 sessions of EECP.[35, 45-47] Although EECP was mostly known to decrease symptoms in patients with angina, its role in the treatment of patients with HF has only recently been investigated. Recent studies suggest that EECP increases exercise capacity and improves functional status and quality of life in patients with HF. On the strength of these findings, FDA cleared EECP therapy for the treatment of HF in 2002.[35-39] In summary, EECP is a very efficient non-invasive technique in that it effectively increases LVEF in moderate heart failure NYHA FC III, II with any etiology.[35,54-56]

In group C (CRT implantation), there was clearly a significant improvement in EF, LVESV, and E/E' ratio after CRT implantation ($P<0.05$). It increased EF significantly after implantation ($P<0.001$) and reduced E/E' ($P<0.001$), which chimes in with the results of all recent large randomized trials.[30] For example, a recent large meta-analysis carried out by Porciani et al. documented the relationship between restored ventricular synchrony in patients treated with CRT and the companion trial. The researchers stated that an improvement in systolic function, which we discussed earlier, was translated within 6 months into reverse remodeling with a sustained increase in EF and a reduction in the LV size.[57] Porciani et al. assessed the effect of CRT on the mechanisms underlying functional mitral regurgitation in HF and showed at 6-month follow-up with echocardiography that there was a 15% reduction in LVESV, reverse remodeling with reduction in LVESV at baseline NYHA class, and quality of life. They also found that all echocardiographic parameters evaluated were similar in their two study groups except for EF, which was significantly lower in responders than in non-responders, and for the Asynch index, which was higher in responders. At follow-up, the responders had 15% LVESV reduction and significant improvement in NYHA class and quality of life ($P<0.001$).[57]

All recent studies have demonstrated that CRT or CRT-D is comparable to optimal pharmacological therapy for the effect on survival and hospitalization. CRT or CRT-D reduces the incidence of the primary end point of all-cause mortality ($P<0.02$), as well as HF hospitalization rates. CRT alone reduces mortality by 24 percent, whereas, CRT-D reduces it by 36 percent.

Among the three groups in our study, significant improvement in LVESV, LVEDV, EF, and E/E' was statistically greater than that in the pharmacological therapy group. Furthermore, there were better results in the CRT groups in comparison with the EECP group, but it was not statistically significant.

## Conclusion

In summary, HF is a multifactorial complication in which ventricular remodeling decreases contractility. The correction of HF to reverse remodeling is a major issue in the management of patients with severe HF. The number of therapeutic options for the care of HF patients is extensive, and access to investigational agents or complex approaches limited to specialized centers such as transplantation, are often required. Disease management programs not only improve survival but also reduce the cost of HF treatment. Attaining this goal requires a strong cooperative effort among the various components of the heart care teams in HF centers, health care delivery organizations, and individual physicians.

Our findings suggest that DMPs or guideline-based treatments reduce first hospitalization and rehospitalization rates in patients with HF and improve NYHA functional class, and the echocardiographic findings of LVESV, LVEDV, LVEF, and E/E' ratio. In the hope of improving HF outcomes, DMPs (medical care, EFCP, CRT-D implantation, etc.) have been developed to standardize and optimize HF treatment, focusing on disease education

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for the patient and continuing support after hospital discharge.

In light of our findings, we suggest that another study be conducted to evaluate the morbidity and mortality of this protocol with at least a 5-year follow-up.

## Conflict of Interest

No conflicts of interest have been claimed by the authors.

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